to the Exocopol, this has been amended to recite the correct term "Exocorpol" which is a well known polyethylene polyoxypropylene which, as can be seen from page 7537,(of the Merck Index filed herewith) is a known surfactant.

Claims 2 to 5, 8 to 11, 14 and 15 were rejected under 35 USC 112, second paragraph, as being indefinite since the basis of the molecular weight was not recited therein and claim 14 was deemed indefinite since a comma had been dropped therefrom. Claim 15 was objected to as being dependent upon a cancelled claim.

Applicants respectfully traverse these grounds of rejection since the amended claims are believed to properly define the invention. The claims have been amended to recite that the molecular weight is based upon the Dalton basis. The comma has been inserted into claim 14 and claim 15 was amended in the amendment of September 11, 2001 to be dependent upon claim 14 and therefore, this objection is not deemed to be proper. Therefore, the amended claims are believed to properly define the invention and withdrawal of these grounds of rejection is requested.

The specification has been amended to indicate that while propylene glycol is used for the production of the

been inserted into claim 14 and claim 15 was amended in the amendment of September 11, 2001 to be dependent upon claim 14 and therefore, this objection is not deemed to be proper. Therefore, the amended claims are believed to properly define the invention and withdrawal of these grounds of rejection is requested.

The specification has been amended to indicate that while propylene glycol is used for the production of the polyoxyethylene- polyoxypropylene, the hydrophobic polyoxypropylene block is no longer a glycol and therefore, reference to the glycol has been deleted from the specification to properly define the same.

With respect to the drawings, Applicants are in the process of obtaining new formal drawings and they will be submitted as soon as possible.

In view of the amendments to the specification and claims and the above remarks, it is believed that the claims clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
Muserlian, Lucas and Mercanti

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Attorney for Applicants
Tel. # (212) 661-8000

CAM:ds
Enclosures

146.1286

MARKED UP PAGES OF SPECIFICATION SHOWING CHANGES MADE

Please replace the paragraphs beginning at page 1, line 6 to line 28 with the following rewritten paragraphs:

--The present invention relates to a cartilage and bone morphogenetic repairing composition for the treatment of bone fracture and bone defect. In more detail, this invention is concerned with the cartilage and bone morphogenetic repairing [material]composition which contains a polyoxyethylene-polyoxypropylene [glycol] and a bone morphogenetic protein.

BACKGROUND OF THE INVENTION

For repairing cartilages and bones, in addition to autoplasty, there has been practiced a procedure in which a prosthetic material for defected sites of cartilage and bone composed of a combination of a bone morphogenetic protein and a suitable carrier was imbedded in the defected site. In practicing this, the defected site can be exposed on surgical operation to apply a cartilage and bone repairing [material] composition containing a bone morphogenetic protein directly to the defeced site, and thus, the materials in a solid form such as blocks, sponges, sheets and the like which are easy to handle have been widely applied. Those in a semisolid form such as gels or pastes can also be used. As

the carriers which made such solid or semisolid forms applicable, there have been utilized, for example, metals such as stainless or titanium alloys or collagen and hydroxyapatite (HAP) ir a nuxytre thereof.?-

Please replace the paragraph bridging pages 3 and 4 with the following:

--The present inventors have made earnest studies on the relationship between the active ingredient, a bone morphogenetic protein, and a carrier therefor in the case of a bone repairing method without surgical operation and have found that a certain class of polyoxyethylene-polyoxypropylene [glycols] can show a high bio-absorption, a good affinity to a bone morphogenetic protein and temperature dependent sol-gel reversible transition. The present inventions have preparaed a bone morphogenetic composition [material] by mixing an aqueous polyoxyethylene-polyoxypropylene [glycol] solution and a bone morphogenetic protein, which is an injectable liquid at a temperature of from 1EC to 30EC at the time of administration and may be gelatinized at around 37EC within 3 minutes after administration. [They have] It has been found that ectopic cartilage and bone morphogenesis are accomplished by administering said [material] composition to mice intramuscularly at the femoral muscle and then retaining a bone m orphogenetic protein at the administration sites in vivo,

the carriers which made such solid or semisolid forms applicable, there have been utilized, for example, metals such as stainless or titanium alloys or collagen and hydroxyapatite (HAP) ir a nuxytre thereof.--

Please replace the paragraph bridging pages 3 and 4 with the following:

--The present inventors have made earnest studies on the relationship between the active ingredient, a bone morphogenetic protein, and a carrier therefor in the case of a bone repairing method without surgical operation and have found that a certain class of polyoxyethylene-polyoxypropylene [glycols] can show a high bio-absorption, a good affinity to a bone morphogenetic protein and temperature dependent sol-gel reversible transition. The present inventions have preparaed a bone morphogenetic composition [material] by mixing an aqueous polyoxyethylene-polyoxypropylene [glycol] solution and a bone morphogenetic protein, which is an injectable liquid at a temperature of from 1EC to 30EC at the time of administration and may be gelatinized at around 37EC within 3 minutes after administration. [They have] It has been found that ectopic cartilage and bone morphogenesis are accomplished by administering said [material] composition to mice intramuscularly at the femoral muscle and then retaining a bone morphogenetic protein at the administration sites in vivo,

upon which this invention has been completed.--

Please replace the paragraph beginning at page 4, line 16 with the following rewritten paragraph:

--This invention is concerned with a cartilage and bone morphogenetic repairing [material] composition which contains a polyoxyethylene-polyoxypropylene [glycol] and a bone morphogenetic protein.--

Please replace the paragraph bridging pages 4 and 5 with as follows:

--The polyoxyethylene-polyoxypropylene [glycol(s)]as used herein is a generic name of nonionic surface active agents of a polymer type having less hydrophilic polypropylene glycols as a hydrophobic group and ethylene oxide as a hydrophilic group. It may be feasible to prepare surface active agents having various properties by changing a molecular wieght of the polypropylene [glycol] and a mixing ratio thereof to the ethylene oxide. The synthesizable-polyoxyethylene-polyoxypropylene [glycols] have a molecular weight of the polypropylene glycol in the range of 900-4,000 and a percent by weight of the ethylene oxide in the total molecule of 5%-90%. For instance, the polyoxyethylene-polyoxypropylene [glycol] block polymers (ADEKA?) manufactured by Asahi Denka Kogyo K.K. are systematically named according to a molecular weight of polypropylene glycol and a weight ratio of the ethylene oxide to be added and the classification list thereof is

shown in Fig.1.--

Please rewrite the first full paragraph of page 5 as follows:

--Industrial utilization of polyoxyethylene-polyoxypropylenes [glycol] includes aperients, ointment bases, artificial blood, coating for tablets, excipients, solubilizers or solubilizing agents for injections and others in the field of pharmaceutics, in addition to the use as general cleaning agents or antifoamings. In particular, Pluronic F-68 (a molecular weight of polypropylene [glycol] of 1,750 and an ethylene oxide content of 80%) has a remarkable antihemolytic action and has been marketed in the name of EXOCOROL? from the Green Cross Corporation (polyoxyethylene-polyoxypropylene glycol) as an additive for extracorporeal circulation of blood. It is apparent from the results of toxicity tests using various animals that polyoxyethylene-polyoxypropylenes have extremely low toxicity and low irritative property, with no reports on possible side-effects such as antigenicity and so on (Fragrance Journal, 7, 82-87, 1974). The results of toxicity tests are shown in Table 1.--

Please replace the paragraphs beginning at page 6, lines 1 to page 7, line 14 with the following rewritten paragraph:

--Polyoxyethylene-polyoxypropylene [glycols] are superior in

terms of handiness to collagen showing non-reversible phase-transition by changes in temperatures in the point that they show reversible sol-gel phase-transition. This property may be controlled by selection of the optimum polyoxyethylene-polyoxypropylene [glycol] for the temperature to develop the phase-transition and by changing the concentration of the aqueous solution of said polyoxyethylene-polyoxypropylene [glycol] (Int. J. Pharm. 22, 207-218, 1984 and EP 0551626A1).

It is obvious from the foregoing that polyoxyethylene-polyoxypropylenes [glycols] have a superior nature as a drug carrier. Attemps have already been made to combine them with a low molecular weight drug such as local anesthetics, anticancer agents and so on (Int. J. Pharm. 8, 89-99, 1981 and Chem. Pharm. Bull. 32, 4205-4208, 1984) and to admix with a high molecular weight physiologically active proten such as interleukins and the like (Pharm. Res. 9, 425-434, 1992).

This invention relates to a cartilage and bone morphogenetic repairing material which contains a polyoxyethylene-polyoxypropylene [glycol] and a bone morphogenetic protein, wherein the [polypropylene] polyoxypropylene [glycol] as a constituent of said polyoxyethylene-polyoxypropylene [glycol] has a molecular weight of about 1,500-4,000 and an ethylene oxide content of about 40-80%/molecule. Within the above ranges, there will be provided the Pluronics capable of performing temeprature-

dependent sol-gel reversible transition, which characterized the present Pluronics.

Moreover, this invention relates to a cartilage and bone morphogenetic repairing composition wherein a concentration of polyoxyethylene-polyoxypropylenes [glycols] as described above in an aqueous solution is about 10-50%. It is known that the reversible phase transition temperature of polyoxyethylene-polyoxypropylenes [glycols] varies in general depending on the concentration of their prepared aqueous solutions, and the polyoxyethylene-polyoxypropylenes [glycols] within the above-mentioned constituent ranges may gelate at around body temperature, i.e. about 37EC at a concentration of about 10-90% in its aqueous solution. As the most preferable example, there is prepared the polyoxyethylene-polyoxypropylene [glycol] block polymer aqueous solution of 15-30% concentration having a molecular weight of [polyropylene glycol] polyoxypropylene of 3,850 and an ethylene oxide content of 70% (Pluronic F-127)--

Please replace the paragraph beginning at page 7, line 19 to page 9, line 1 with the following rewritten paragraphs:

--The bone morphogenetic proteins used in the this invention include, but are not limited to, a series of proteins belonging to the TGB-ß gene superfamily such as BMP-2 to BMP-9 and so on, the

protein named MP52, the protein named GDF-5 and the like. Particularly preferable BMP-2 is a protein produced using Chinese hamster ovary (CHO) cells according to the genetic engineering technology reported by Wang, et al. (Proc. Natl. Acad. Sci, USA 87, 2220-2224, 1990 and U.S. Patent No. 4,877,864), and particularly preferable MP52 is a new protein produced according to the genetic engineering technology suggested by the present inventors (our copending Japanese Patent Application [No. 93644/1995) Serial No. 531,621 filed October 20, 1977). This new protein can be produced by constructing a plasmid containing the DNA sequence coding the amino acid sequence as shown in SEQ ID No: 1 of the Sequence Listing derived from MP52 described in said Japanese patent application and having added the codon coding methionine at the N-terminal of said DNA sequence; transforming the plasmid into E.coli; incubating the E.coli to obtain an inclusion body; and solubilizing and purifying the inclusion body to obtain a monomer protein, which is then dimerized and purified.

An aqueous solution of 15-30% polyoxyethylene-polyoxypropylene [glycol]block polymer containing as an active ingredient BMP-2 or MP52 was intramuscularly injected to mice at the femoral muscle. MP52 was retained at the administered sites and then an ectopic cartilage and bone morphogenesis ability was observed in vivo.

There has not yet been reported to date an injectable

cartilage and bone morphogenetic repairing material comprising a polyoxyethylene-polyoxypropylene [glycol] in combination with a bone morphogenetic protein which may be useful for repair of cartilage and bone, especially as a treating agent for bone fracture.

The present invention is further concerned with a cartilage and bone repairing agent containing a polyoxyethylene-polyoxypropylene [glycol] and a bone morphogenetic protein.

Moreover, the present invention is concerned with a method of treatment for a cartilage and bone repairing, by which a cartilage and bone morphogenetic repairing composition comprising a polyoxyethylene-polyoxypropylene in combination with a bone morphogenetic protein which may be useful for repair of cartilage and bone, especiallly as a treating agent for bone fracture.

The present invention is further concerned with a cartilae and bone repariing composition contaiing polyoxyethylene-polypropylene and a bone morphogenetic protein.

Moreover, the present invention is concerned with a method of treatment for a cartilage and bone repairing, by which a cartilage and bone morphogenetic composition comprising a polyoxyethylene-polyoxypropylene in combination with a bone morphogenetic protein is administered locally to the site of bone fracture or bone

defect of human or animal.--

Please amend the paragraph beginning at page 9, line 2 as follows:

--BRIEF DESCRIPTION OF THE DRAWINGS:

Fig 1 is a classification figure for ADEKA® Pluronics, wherein an ethylene oxide content in terms of % by weight in a total molecule of a polyoxyethylene-polypropylene [glycol] is indicated on the abscissa, while a molecular weight of the component polypropylene [glycol] in a polyoxyethylene-polyoxypropylene [glycol] is indicated on the ordinate.—

Please rewrite the paragraph in lines 4 to 17 of page 10 as follows:

--ADEKA® Pluronic F-127 (Asahi Denka Kogyo K.K.) is known to be one of the least toxic polyoxyethylene-polyoxypropylenes [glycols] ("SEIYAKU KOJO" 6, 875-880, 1986). In 7.0 g of distilled water for injection was dissolved under ice-cooling 3.0 g of ADEKA® Pluronic F-127 to prepare a 30% aqueous solution of ADEKA® Pluronic F-127. The aqueous solution of ADEKA® Pluronic F-127 was poured portionwise under ice-cooling to a 96-well titer plate at 360 μl/well, 40 μl of 0.01 N HCl containing 80 μg of BMP-2 was added to each well and mixed. The mixture was sterilized by

passing through a 0.22 μm filter at 4EC to form a BMP-2 injection of a total volume of about 400 μl (a final concentration of ADEKA® Pluronic F-127 of 27%). Similarly, the BMP-2 injections having final concentrations of ADEKA® Pluronic F-127 of 10, 15, 18 and 22.25% were prepared.--

Please rewrite the paragraph of lines 8 to 13 of page 12 as follows:

--It was clearly shown in Table 2 that MP52 when [a]polyoxyethylene-polyoxypropylenes [glycols] were used as a pharmaceutical carrier could apparently be retained more as compared with the case where a simple MP52 aqueous solution was injected. Also similar results were obtained using the injection of Example 1.--

Please rewrite the paragraph of lines 16 to 18 of page 13 as follows:

--From the aforesaid results, safety and usefulness of a polyoxyethylene-polyoxypropylene [glycol] were confirmed when used as a carrier for the bone forming factor.--

MARKED UP VERSION OF CLAIMS SHOWING CHANGES MADE

Claim 2 (thrice amended) The cartilage and bone morphogenetic repairing composition as claimed in claim 14, wherein the [polypropylene glycol] polyoxypropylene as a constituent of said polyoxyethylene-polyoxypropylene [glycol] has a molecular weight of about 1,500-4,000 in a unit of dalton and the ethylene oxide content is about 30-80% per molecule.

Claim 3 (amended) The cartilage and bone morphogenetic repairing [material] composition as claimed in claim 2, wherein [a] the concentration of said polyoxyethylene-polyoxypropylene [glycol] in [an] the aqueous solution is about 10-50%.

Claim 8 (twice amended) The method of claim 15 wherein the [polypropylene glycol] polyoxypropylene as a constituent of the polyoxyethylene-polyoxypropylene [glycol] of said composition has a molecular weight of about 1,500 to 4,000 in a unit of dalton and the ethyleneoxide content of the polyoxyethylene-polyoxypropylene [glycol] is about 40 to 80% per molecule.

Claim 9 (twice amended) The method of claim 8 wherein the polyoxyethylene-polyoxypropylene [glycol] is about 10 to 50% by weight of the aqueous solution.

Claim 14 (four times amended) A cartilage and bone morphogenetic repairing composition comprising a collagen-free aqueous solution of a polyoxyethylene-polyoxypropylene [glycol] and an effective amount of a bone morphogenetic protein, the molecular weight of polyoxypropylene [glycol] as a constituent of said polyoxyethylene-polyoxypropylene [glycol] molecular is 900 to 4,000 in a unit of dalton and the ethylene oxide content is 5 to 90% by weight of the polyoxyethylene-propoxypropylene [glycol] molecule whereby the solution is aqueous at 1 to 30EC and gelatinizes at about 37EC.

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

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1989

The first radioactive substance discovered
n 1898. A product of disintegration of
s contained in about 25,000 tons of pitchb
radium that is more than 30 years old.
f a deposit on a bismuth plate immersed in a
loride: Marckwald, *Ber.* 35, 2285 (1902);
old or nickel plate: Curie, Joliot, *J. Chim.*
931); Haissinsky, *ibid.* 33, 97 (1936);
Ital. 66, 797 (1936); Ziv, *C. R. Acad. Sci.*
939). Obtained in the metallic form by
ickel on a collodion film: Rollier *et al. J.*
(1936). The only readily accessible isotope
imate member of the radium decay series,
Radium F (Ra-F). Decays by α-emission
to $^{206}_{82}$Pb. Comprehensive reviews: K.
istry of the Rare Radioelements (Butterworths,
idem, Endeavour 22(86), 61 (May 1963);
Tellurium and Polonium" in *Comprehensive*
istry vol. 2, J. C. Bailar, Jr., et al., Eds.
Oxford, 1973) pp 935-1008.
o allotropic forms; coexist between 15°
rm) 9.196; d (β-form) 9.398. mp 254°; bp 9
of vaporization: 24.597 kcal/mole.
= 42 μohm-cm at 0°; β-Po = 44 μohm-cm
cal properties: Maxwell, *J. Chem. Phys.*
)). Chemically resembles tellurium and
is a volatile, unstable hydride, PoH_2. Forms
Na_2Po; a carbonyl PoCO; a hydroxide Po(OH)
ution: Radiation hazard; alpha emitter. Sol
-d to kidneys, spleen; insol, airborne compds
. Max permissible concn of insol $^{210}_{84}$Po in
μ-Curie/cc, *National Bureau of Standards*
'9 (1959).

534. Polonium Dioxide. O_2Po; mol wt
%, Po 86.72%. PoO_2. Formed from the
: Martin, *J. Phys. Chem.* 58, 911 (1954).
vo crystal modifications: yellow, low temp
-centered cubic symmetry; red, high-temp
gonal symmetry. Darkens in color on heating
brown at sublimation temp of 885°. Dec
ts at 500° under vacuum; slowly reduced to
ogen at 200°. Heat of formation ~30 kcal/
olns of ammonium carbonate, phosphoric

7535. Polonium Tetrachloride. Cl_4Po; mol
0.42%, Po 59.58%. $PoCl_4$. May be prepd by
allic polonium in hydrochloric acid; by heating
ide in carbon tetrachloride vapor at 200°; by
al in dry chlorine at 200°; also by heating the
hydrogen chloride, thionyl chloride vapor, or
rus pentachloride: *Review:* K. W. Bagnall,
Rare Radioelements (Butterworths, London,
lygroscopic, bright yellow, cryst solid.
linic. Hydrolyzed by moist air, forming a
efinite composition. mp ca 300° (in chlorine
red at 350°. bp 390°. Vapors are purple-
e-green above 500°. Sol in water (fairly slow
ely sol in hydochloric acid, thionyl chloride,
in ethanol, acetone. Dec by dil nitric acid.
nplex with two moles of tributyl phosphate.

7536. Poloxalene. *Methyloxirane polymer*
ly(oxyethylene)-poly(oxypropylene)-poly
lymer; bis[hydroxyethylpoly(ethyleneoxy)ethyl
neglycol; dipolyoxyethylated polypropylene
yethylene oxypropylene polymer; SK & F
iard; Theraboat. A block polymer of ethylene
opylene oxide, with a mol wt of approx 3000
epn: Lundsted, U.S. pat. 2,674,619 (1954
iem.). Field trial in wheat pasture bloat of
irtley *et al., J. Animal Sci.* 41, 752 (1975).
cretion in rats: J. B. Rogers *et al., Drug Metab.*
1 (1984). Hypocholesterolemic effect in rabbits
lin. Invest. 71, 1490 (1983); *eidem, Atherosclerosis*
e.) 64, 37 (1987). *Review:* Stanton, *Am. Perfum.*
, No. 4, 54, 56, 58 (1958). *See also* Poloxamers.

$HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_cH$

Average values for a, b, c are:
a = 12; b = 34; c = 12

nonionic surfactant polymer.
Pharmaceutic aid (surfactant).
VET): Prevention of bloat in cattle.

Poloxamers. *Methyl oxirane polymers, polymer with polyethylenepolypropylene glycols, polymers; α-hydroxypoly(oxyethylene)poly(oxypropylene)-poly(oxyethylene) block copolymers; Pluronics.* Series of surfactants with the structure $HO(CH_2CH_2O)_a(CH_2CH(OH)CH_2O)_b(CH_2CH_2O)_cH$ where b is at least 15 and $(CH_2CH_2O)_{a+c}$ is varied from 20 to 90% by weight. Mol wt from 1000 to greater than 16,000. The poly(oxypropylene) segment is hydrophobic; the poly(oxyethylene) segment hydrophilic. Comprehensive reviews: I. R. Schmolka, *Am. Perfumer Cosmet.* 82(7), 25-30 (1967); *idem* "Ethylene Oxide Block Copolymers" in *Nonionic Surfactants* M. Schick, Ed. (Dekker, New York, 1967) pp 300-. Also Poloxalene.

Liquids, pastes or flakeable solids. Relatively hydrophilic. Vary from water-insoluble to very water-soluble; more sol in cold than hot water. In general, sol in polar solvents (benzene, toluene, xylene), chlorinated solvents, acetone, alc, propylene or hexylene glycol, butyl carbitol, methyl ethyl ketone, cyclohexanol; insol in ethylene glycol, kerosene, mineral oil. Low-foaming properties. Stable to acids, alkalies, metallic ions.

182LF, Pluronic L62LF. a = 7, b = 30, c = 2; mol wt 2450. Low-foaming liquid. d_{25}^{25} 1.035. Brookfield viscosity (25°) 375 cp; cloud pt (10% aq soln): 22°.

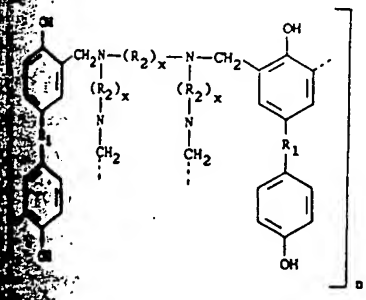
188, poloxalkol (obsolete), Exocorpol, Pluronic F-68. a = 75, b = 30, c = 75; av. mol wt 8350. Flakeable solid, 50° (minimum); cloud pt (10% aq soln): > 100°.

331, Pluronic L101. a = 7, b = 54, c = 7; av. mol wt 3800. Liquid. d_{25}^{25} 1.018; Brookfield viscosity (25°): 1000 cp; cloud pt (10% aq soln): 11°.

Used as additives; defoamers; antistatic agents; demulsifiers, wetting agents, gelling agents; emulsifiers; solubilizers; dispersants; dye levelers.

USE: Poloxamer 182LF as pharmaceutic aid; 188

Polyamine-Methylene Resin. Resinat; Exorbin. Condensation product with polyamines. An ion-exchange resin specially purified for medicinal use.



granular, free-flowing powder. Insol in water, aq solns of acids and alkalies. Under the conditions of the old N.N.R. assay for acid-consuming capacity, less than 50 ml 0.1*N* hydrochloric acid is consumed by 2 g of the resin.

USE: Antacid.

Polybenzarsol. *(4-Hydroxyphenyl)arsonic acid polymer with formaldehyde;* Benzodol. A polymeric mixture prepd by heating formaldehyde (40%) (0.116 mole) over a period with *p*-hydroxybenzenearsonic acid (0.209 mole) in 50% H_2SO_4 at 0-5° and keeping it cold for 21 hrs. The reaction mixture with H_2O precipitates the product:

Faith, *J. Am. Chem. Soc.* 72, 837 (1950). Description: Jones *et al., Antibiot. & Chemother.* 8, 400 (1958).

White powder. Somewhat sol in water; sol in alcoholic NaOH. LD_{50} i.p. in mice: 235 mg/kg. No deaths after 4 g/kg i.g. in mice.

THERAP CAT: Antiamebic.

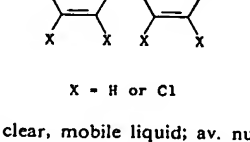
7540. Polybrominated Biphenyls. PBB's; brominated biphenyls; polybromobiphenyls. Mixtures with structures similar to polychlorinated biphenyls, *q.v.*, where each X = H or Br. Once widely used commercially. Prepn: H. Hahn *et al.*, Ger. pat. 1,161,547 (1964 to Chem. Fabrik Kalb); G. A. Burk, U.S. pat. 3,733,366 (1973 to Dow); L. C. Mitchell, D. R. Breckenridge, U.S. pats. 3,763,248 and 3,833,674 (1973, 1974 both to Ethyl Corp.). Persistence in soils: L. W. Jacobs *et al., J. Agr. Food Chem.* 24, 1198 (1976). Photodegradation: L. O. Ruzo *et al., ibid.* 1062. Review of environmental hazards: K. Kay, *Environ. Res.* 13, 74-93 (1977); F. J. DiCarlo *et al., Environ. Health Perspect.* 23, 351-365 (1978).

Firemaster BP-6, major component is *2,2',4,4',5,5'-hexabromobiphenyl.* Softens at 72°, dec above 300°. Low vapor pressure; degraded by uv light. Very sol in benzene, toluene. Insol in water.

Note: The 1973 "Michigan Incident" in which BP-6 was accidentally added to animal feed, and resulted in widespread destruction of contaminated farm animals, led to the removal of BP-6 from the market: L. J. Carter, *Science* 192, 240 (1976). This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 169.

USE: Flame retardant.

7541. Polychlorinated Biphenyls. PCBs; chlorinated biphenyls; chlorobiphenyls; Aroclor; Clophen; Fenclor; Kanechlor; Phenoclor; Pyralene; Santotherm. Once widely used industrial chemicals whose high stability contributed to both their commercial usefulness and their long-term deleterious environmental and health effects. Early synthesis: H. Schmidt, G. Schulz, *Ann.* 207, 338 (1881). Commercially available since 1930: C. Penning, *Ind. Eng. Chem.* 22, 1180 (1930). Commercial PCBs are mixtures. The Aroclors are characterized by four digit numbers. The first two digits indicate that the mixture contains biphenyls (12), triphenyls (54) or both (25, 44); the last two digits give the weight percent of chlorine in the mixture (e.g. Aroclor 1242 contains biphenyls with approx 42% chlorine). Reviews of environmental impact and toxicity: L. Fishbein, *Ann. Rev. Pharmacol.* 14, 139-156 (1974); R. D. Kimbrough, *CRC Crit. Rev. Toxicol.* 2, 445-498 (1974); *National Conference on Polychlorinated Biphenyls,* Nov. 19-21, 1975 (EPA-560/6-75-004, 1976) 487 pp. Accumulation of airborne PCBs in foliage: E. H. Buckley, *Science* 216, 520 (1982). *Reviews:* H. L. Hubbard in *Kirk-Othmer Encyclopedia of Chemical Technology* vol. 5 (Interscience, New York, 2nd ed., 1964) pp 289-297; O. Hutzinger *et al., The Chemistry of PCB's* (CRC Press, Cleveland, Ohio, 1974) 269 pp; J. W. Lloyd *et al., J. Occup. Med.* 18, 109-113 (1976). Review of carcinogenicity studies: *IARC Monographs* 18, 43-103 (1978).



X = H or Cl

Aroclor 1242, clear, mobile liquid; av. number Cl/molecule: 3.10. d_4^{25} 1.381, $d_4^{15.5}$ 1.392. Distillation range 325-366°. Flash point (open cup) 348-356°F. n_D^{20} 1.627-1.629. Dielectric constant (1000 cycles) 5.6 (25°), 4.9 (100°).

Aroclor 1254, light yellow, viscous liquid; av. number Cl/molecule: 4.96. d_4^{65} 1.495; $d_4^{15.5}$ 1.505. Distillation range 365-390°. No open cup flash point to boiling. n_D^{20} 1.629-1.641. Dielectric constant (1000 cycles) 5.0 (25°), 4.3 (100°). LD_{50} orally in weanling rats: 1295 mg/kg (Kimbrough).

Aroclor 1260, light yellow, soft, sticky resin; av. number